

Inderide®
(propranolol hydrochloride [Inderal®]
and hydrochlorothiazide)
CI 4982-3

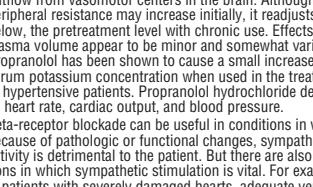


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Rx only

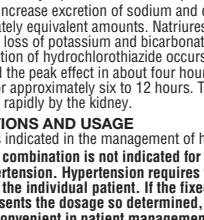
DESCRIPTION

Inderide Tablets for oral administration combine two antihypertensive agents: Inderal (propranolol hydrochloride), a beta-adrenergic blocking agent, and hydrochlorothiazide, a thiazide diuretic-antihypertensive. Inderide 40/25 Tablets contain 40 mg propranolol hydrochloride and 25 mg hydrochlorothiazide; Inderide 80/25 Tablets contain 80 mg propranolol hydrochloride and 25 mg hydrochlorothiazide. Inderal (propranolol hydrochloride) is a synthetic beta-adrenergic receptor-blocking agent chemically described as 1-(Isopropylamino)-3-(1-naphthoxy)-2-propanol hydrochloride. Its structural formula is:



Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.81.

Hydrochlorothiazide is a white, or practically white, practically odorless, crystalline powder. It is slightly soluble in water; freely soluble in sodium hydroxide solution; sparingly soluble in methanol; insoluble in ether, chloroform, benzene, and dilute mineral acids. Its chemical name is: 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its structural formula is:



The inactive ingredients contained in Inderide Tablets are lactose, magnesium stearate, microcrystalline cellulose, stearic acid, and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Propranolol hydrochloride (Inderal®)

Propranolol hydrochloride is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by propranolol, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately metabolized by the liver on its first pass through the portal circulation. Peak effect occurs in one to one-and-one-half hours. The biological half-life is approximately four hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range, as observed in clinical practice, is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

The mechanism of the antihypertensive effect of propranolol has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasoconstrictor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to, or below, the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. Propranolol has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients. Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure.

Beta-receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive, which should be preserved. In the presence of AV block greater than first degree, beta blockade may prevent the necessary facilitatory effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity, which should be preserved in patients subject to bronchospasm.

The proper objective of beta-blockade therapy is to decrease adverse sympathetic stimulation, but not to the degree that may impair necessary sympathetic support.

Hydrochlorothiazide

Hydrochlorothiazide is a benzothiadiazine (thiazide) diuretic closely related to chlorothiazide. The mechanism of the antihypertensive effect of the thiazides is unknown. Thiazides do not affect normal blood pressure.

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage, all thiazides are approximately equal in their diuretic potency.

Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate. Onset of diuretic action of hydrochlorothiazide occurs in two hours, and the peak effect in about four hours. Its action persists for approximately six to 12 hours. Thiazides are eliminated rapidly by the kidney.

INDICATIONS AND USAGE

Inderide is indicated in the management of hypertension. This fixed combination is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management.

CONTRAINDICATIONS

Propranolol hydrochloride (Inderal®)

Propranolol is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block;

3) bronchial asthma; 4) congestive heart failure (see "WARNINGS") unless the failure is secondary to a tachyarrhythmia treatable with propranolol.

Hydrochlorothiazide

Hydrochlorothiazide is contraindicated in patients with anuria or hypersensitivity to this or other sulfonamide-derived drugs.

WARNINGS

Propranolol hydrochloride (Inderal®)

Cardiac Failure. Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. Propranolol acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by propranolol's negative inotropic effect. The effects of propranolol and digitalis are additive in depressing AV conduction.

Patients Without a History of Heart Failure. Continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during propranolol therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given additional diuretic, and the response observed closely; a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, propranolol therapy should be withdrawn (gradually, if possible); b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

Angina Pectoris. There have been reports of exacerbation of angina and, in some cases, myocardial infarction following abrupt discontinuation of propranolol therapy.

Therefore, when discontinuation of Inderide is planned, the dosage should be gradually reduced and the patient should be carefully monitored. In addition, when propranolol is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If propranolol therapy is interrupted or exacerbation of angina occurs, it usually is advisable to reinstitute propranolol therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema): PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS.

Propranolol should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

Beta-Surgery. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Propranolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin. Hypoglycemic attack may be accompanied by a precipitous elevation of blood pressure in patients on propranolol. Propranolol therapy, particularly in infants and children, diabetic or not, has been associated with hypoglycemia especially during fasting as in preparation for surgery. Hypoglycemia also has been found after this type of drug therapy and prolonged physical exertion and has occurred in renal insufficiency, both during dialysis and sporadically, in patients on propranolol. Acute increases in blood pressure have occurred after insulin-induced hypoglycemia in patients on propranolol.

Thyrotoxicosis: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of thyrotoxicosis, including thyroid storm. Propranolol may change thyroid-function tests, increasing T₄ and reverse T₃, and decreasing T₃.

Wolf-Parkinson-White Syndrome: Several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

Hypokalemia. Hypokalemia may be precipitated by the drug and interfere with the therapeutic effect of diuretics. Such interference may occur in patients with a history of digitalis or peripheral adrenergic-blocking drugs.

Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

PRECAUTIONS

General

Propranolol should be used with caution in patients with impaired hepatic or renal function. Inderide is not indicated for the treatment of hypertensive emergencies.

Risk of anaphylactic reaction. While taking beta blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such reactions used to be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Hypokalemia. Hypokalemia may develop, especially with bruisures or when severe cirrhosis is present.

Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability).

Any chloride deficit is generally mild, and usually does not require specific treatment except under extraordinary circumstances (as in liver or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hypercalcemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Diabetes mellitus which has been latent may become manifest during thiazide administration.

If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy.

Calcium excretion is decreased by thiazides. Pathologic changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulceration, have not been seen.

Information for Patients

Beta-adrenergic receptor blockade can cause reduction of intraocular pressure. Patients should be told that Inderide may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

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